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August 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5230 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Federal Register Notice June 28, 1999 (FR Vol 64, No. 123, Page 34660)

Docket No. 99D-0529

Dear Colleague:

Baxter Healthcare Corporation is submitting comments on the draft FDA Guidance for Industry on "*Changes to an Approved NDA or ANDA*", released for comment on June 28, 1999. General comments are presented first, followed by specific comments with reference to the applicable line numbers.

Baxter Healthcare will also be submitting separate comments on the proposed rule under Docket No. 99N-0193.

General Comments:

1. Baxter fully supports the Agency's initiatives to streamline the regulatory process for reporting and implementing post-approval changes, which we believe, will facilitate continuous improvement of our products. However, Baxter does not believe that the reporting recommendations outlined in the proposed guidance will result in significant regulatory relief. While the structure of the proposed guidance suggests more flexibility, many of the examples FDA has cited will actually result in increased reporting requirements compared to current industry practice. Examples are given in our specific comments.
2. Several examples given in this guidance seem to require the submission of quality control information that is already provided for in 21 CFR §211 and therefore subject to field inspection. Such instances are identified in

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our specific comments. We recommend that requirements that are already provided for in 21 CFR §211 not be required to be reported as a post-approval change.

3. The guidance states that the terms "*validate*" and "*validation*", as used by FDA in this guidance, are intended to mean assessing the change and, are not intended to mean the same as cGMP validation. However, we believe that inconsistent use of the same terms for different regulatory meanings lends itself to unnecessary confusion. The terms "*validate*" and "*validation*" should be replaced by "*assess*" and "*assessment*".
4. The use of broad or vague terms (i.e., "*any change*" and "*may impact*") should be minimized. Such terms lend themselves to different interpretations and are likely to cause confusion and inconsistent application of the guidance.

Specific Comments:

Lines 82-83

There could be circumstances where a comparability protocol(s) is submitted and approved as part of an original application. We recommend adding the phrase, "*if not approved as part of the original application*" following "A proposed comparability protocol".

Lines 97-100

These two sentences are specific to labeling changes and should be deleted from the general requirements section. These statements more appropriately appear in lines 717-719 and 745-747 in section "10. Labeling."

Lines 104-114

We recommend replacing the terms "*validate*" and "*validation*" with "*assess*" or "*assessment*" throughout the draft guidance document.

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Line 154

Change “B. Equivalency” to “3. *Comparability*” for clarification and format consistency.

Line 167

Change “C. Adverse Effect” to “4. *Adverse Effect*” for format consistency.

Lines 197-340

We found the use of the terms “sites, facilities, establishments and campuses” to be inconsistent and confusing. We recommend consistency in, and clarification of, the various terms used.

Lines 213-215

We recommend that item (2) be deleted. The important consideration for this type of change is whether the facility has a satisfactory cGMP inspection for the type of operation being moved which is covered under item (3). In addition, the phrase “at some time it has been discontinued” is too vague and lends itself to inconsistent interpretation.

Lines 251-252

We recommend that the phrase “but at some time it had been discontinued and is now being restarted” be deleted. The important consideration for this type of change is whether the facility has a satisfactory cGMP inspection for the type of operation being moved which is already stated in this item. In addition, the proposed phrasing is too vague and lends itself to inconsistent interpretation.

Line 259

We recommend that item (2) be deleted as cross-contamination is appropriately regulated through field inspections under 21 CFR §211.176.



Lines 288-291

This change should be categorized as a Minor Change reported in an Annual Report. This type of change has minimal potential to have an adverse impact since the criteria that the site has a satisfactory cGMP inspection for the type of operation being performed is already met. A requirement to report such changes via a 30-day CBE supplement would represent an increase in reporting requirements over current practice.

Lines 294-300

This type of change should be categorized as a Minor Change reported in an Annual Report. This type of change has minimal potential to have an adverse impact.

Lines 333-334

We recommend deleting this item. Building changes are already covered in lines 319-322. Reporting of other minor changes to simple floor plans are not warranted, represent an increase in reporting requirements over current practice, and are subject to review during field inspections.

Lines 349-351

Delete the sentence "This potential exists because ... rule out such adverse effects." This statement infers that the applicant is not capable of adequately evaluating the potential adverse effects of a change.

Line 357

The phrase "changes may affect sterility assurance" is too broad and all encompassing. We recommend modification of this phrase to "changes that may *significantly impact* sterility assurance".

Line 370

The proposed wording is too broad. We recommend rewording the phrase "Changes that may affect" to "Changes that may *significantly impact*".

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Line 374

As proposed, the wording for this requirement is too broad and could significantly increase the regulatory burden by causing filing of very minor changes as preapproval supplements. We recommend changing "...substitution of steps..." to "...substitution of *significant* steps..."

Lines 376-379

We recommend rephrasing this item as follows to clarify that the change being assessed is a change in process not equipment.

"Replacing sterilizers which operate by one set of principles with sterilizers that operate by another principle (e.g., substituting *a* gravity displacement steam *process* with *a* superheated water spray *process*)."

Lines 380-383

This type of change should be considered a Moderate Change (Supplement - Changes Being Effected). The information required to assess the impact of this type of change would consist of the analogous information submitted to support the original application.

Line 392

We recommend deleting the phrase "into additional aseptic filling shifts."

Lines 398-399

We believe that changes in sterilizer load configurations that do not result in a change outside of the previously validated sterilization process parameters can be adequately reviewed during field inspections. As currently stated, the proposed requirement would result in a significant number of supplements thus increasing the regulatory burden on industry. We recommend the following revised wording:

"Changes in sterilizer load configurations that *result in a change(s)* outside of the *previously validated sterilization process parameters*."

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Lines 400-401

For clarification, "*for aseptic processes*" should be added following "Changes to filtration parameters" and "*pore*" should be inserted between "filter" and "size."

Line 416

Add the word "*significant*" before "process change",

Line 419

Add the word "*adversely*" before "affect".

Line 433

Add the word "*significant*" before "change".

Lines 438-439

For clarification, "Changes to filtration parameters" should be reworded as "*Significant* changes to filtration parameters *for aseptic processes*" and "*pore*" should be inserted between "filter" and "size."

Lines 458-459

Delete "do not require additional aseptic filling shifts or".

Lines 538-539

Minor, insignificant changes and corrections are routinely made to regulatory analytical procedures (e.g. typographical errors, clarifications). We recommend changing this sentence to read "Any changes in a regulatory analytical procedure *which impact the method validation package*, other than those identified as major changes."

Lines 551-562

We believe that the types of changes described in these sections should be re-categorized as Minor Changes to be reported in the Annual Report since the

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reason they are being made is to provide increased assurance of identity, strength, quality, purity, or potency.

Lines 567-571

As proposed, this section would increase regulatory reporting requirements over current practice and will result in inconsistent standards for the same products. It is more appropriate and reasonable to use the compendial review and comment process to resolve inconsistencies/differences between compendial and FDA requirements. This section should be revised to read "Any change made to comply with an official compendium."

Lines 584-585

This requirement would result in increased regulatory reporting requirements over current practice and should be deleted.

Lines 591-595

Delete these lines which infer that the applicant is not capable of adequately evaluating the potential adverse effects of a change.

Line 599-600 and 616

Clarification of the phrase "with that particular dosage form" is needed. Is it intended to mean a particular product (e.g. 5% Dextrose Injection) or a product family (e.g. sterile infusion solution)?

Line 626

Change "may affect" to "may *significantly impact*."

Lines 638-639

As currently worded, this requirement is too broad. We recommend changing this sentence to read "*Significant* change in the size and/or shape of a container for a sterile drug substance or sterile drug product *which impacts sterility assurance*."

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Line 649

We recommend adding the following example: “b. Significant change in the size and/or shape of a container for a sterile drug substance or sterile drug product *which does not impact sterility assurance.*”

Lines 711-713

This requirement would result in increased regulatory reporting requirements over current practice and should be deleted.

After Line 767

Add: “4. Changes made to comply with an official compendium.” which reflects current practice.

Lines 776-777

This sentence is redundant and should be deleted to avoid confusion since this requirement is already stated in Line 370.

Line 778

Add “*if not already approved in the original application*” to the end of the sentence.

Lines 781 and 791

Delete the phrases “based on pilot scale batch data.” and “on full production batches”, respectively. The Agency’s proposed wording would result in requirements incremental to current 21 CFR §314.70(b)(2)(ix) and §314.70(d)(5) which do not require that data be from full production batches.

Line 793

Add “*or tests*” after “Addition of time points”. Adding a test to a stability protocol would provide increased assurance that the product will meet requirements for identify, strength, quality, purity, or potency.

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After Line 793

We recommend the following addition:

“3. Deletion of time points beyond the approved expiry.”

The original protocol approved in an application may include test intervals beyond the approved expiry. As real time data become available and are evaluated, longer expiry dating may not be feasible and continued testing at intervals beyond the approved expiry becomes unnecessary.

Lines 794 – 799

The section pertaining to reference standards should be deleted as it is more stringent than current industry practice and the potential to increase the regulatory burden is unwarranted.

Line 806

Definitions should be added for “Comparability Protocol”, “Campus”, “Site”, “Facility”, and “Establishment”.

Line 865

We recommend changing “i.e., tests, analytical procedures” to “i.e., *list of* tests, *references to* analytical procedures” for consistency with the ICH definition.


Line 869

Replace “validate” with “assess” as previously discussed in these comments.

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Baxter appreciates the opportunity to comment on this important draft guidance. If you have any questions regarding our comments, please contact Pat Barsanti at (847) 270-4643 or me.

Sincerely,

A handwritten signature in cursive script that reads "Marcia Marconi".

Marcia Marconi

Vice President

Regulatory Affairs

(847) 270-4637

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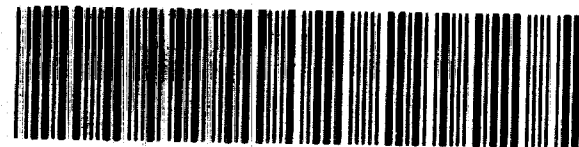
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